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Exercise hemodynamic evaluation in the management of dasatinib-related pulmonary arterial hypertension: a case report

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Abstract

Background Dasatinib-related pulmonary arterial hypertension is a rare complication of chronic therapy for hematological malignancies. Pulmonary hypertension often persists despite drug discontinuation and might require vasodilators. Normalizing pulmonary hemodynamics and avoiding the long-term use of vasodilators is challenging.

Case presentation Patient was a 55-year-old Japanese man complaining of progressive dyspnea on effort and fatigue. He had a history of hypertension and chronic myeloid leukemia treated with dasatinib. He was diagnosed with dasatinib-related pulmonary arterial hypertension by a right heart catheterization at rest, demonstrating a mean pulmonary artery pressure of 31 mmHg and a normal pulmonary arterial wedge pressure of 6 mmHg. Symptoms and hemodynamics significantly improved after the discontinuation of dasatinib and the initiation of upfront combination therapy of vasodilators. An exercise right heart catheterization, performed more than 2 years after the initiation of vasodilators, showed a mean pulmonary artery pressure of 15 mmHg at rest and 29 mmHg at peak exercise (normal reference value, < 30 mmHg), suggesting normal pulmonary microcirculation. On the basis of these findings, pulmonary vasodilators were discontinued. Notably, a repeat exercise right heart catheterization demonstrated preserved pulmonary microcirculation, and the patient has remained asymptomatic for more than 2 years after discontinuing pulmonary-arterial-hypertension-targeted therapy.

Conclusions The evaluation of pulmonary microcirculation by exercise right heart catheterization can be useful for withdrawing pulmonary vasodilators safely in the management of patients with dasatinib-related pulmonary arterial hypertension.

Keywords Case report, Dasatinib, Drug-induced, Exercise-induced pulmonary hypertension, Pulmonary arterial hypertension

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Introduction

Dasatinib-related pulmonary arterial hypertension (PAH) is a rare complication of chronic dasatinib therapy [1]. The cornerstone of the treatment is discontinuing dasatinib and substituting another tyrosine kinase inhibitor since dasatinib induces partially reversible pulmonary arterial disorders [1, 2]. Cessation of dasatinib leads to notable symptomatic improvement, but pulmonary hypertension remains in some patients, and the use of pulmonary vasodilators are required. However, long-term use of PAH medications may lead to related adverse effects and a significant cost burden on the healthcare system. Thus, the attempt to discontinue pulmonary vasodilators is clinically relevant from the perspective of patients' quality of life and health care costs. A previous case of dasatinib-related PAH treated with upfront combination therapy was reported to remain asymptomatic after discontinuing PAH-specific therapy in the short-term follow-up [3]. In contrast, one patient in the French Registry of dasatinib-related PAH described worsening PAH after the withdrawal of pulmonary vasodilators [4]. Therefore, the development of objective criteria is warranted to discontinue pulmonary vasodilators safely.

Incremental exercise tests with repeated hemodynamic measurements provide the most clinical information to detect abnormal pulmonary microcirculation and to inform the selection of treatment [5, 6]. Exercise stress testing for the diagnosis of early stage pulmonary hypertension (PH) has been gaining acceptance [7]. Therefore, pulmonary hemodynamic evaluation during exercise can be useful in detecting early pulmonary vascular dysfunction in a patient with dasatinib-related PAH. Here, we present the case of a patient with dasatinib-related PAH treated with upfront combination therapy, who could safely withdraw pulmonary vasodilators on the basis of exercise hemodynamic evaluation.

Case presentation

This study was approved by the Ethics Committee of Keio University hospital. The patient's clinical course is summarized in Fig. 1. A 52-year-old Japanese man was diagnosed with chronic myeloid leukemia (CML) and started a daily regimen of 100 mg dasatinib. The patient responded favorably, achieving a major molecular response on quantitative reverse transcription polymerase chain reaction, and continued to take dasatinib with good drug adherence and no progression of CML. A total of 36 months after initiation of dasatinib, at the age of 55 years, he presented to our hospital's emergency department with worsening exertional dyspnea and fatigue over the past 2 days. He had a history of hypertension, chronic kidney disease, and obstructive sleep apnea with no psychosocial–economic factors, family history of PAH, or other cardiovascular diseases. The patient was tachypneic with jugular venous dilatation and presented with fever and inflamed skin on the belly, suggesting cellulitis. His lung sounds were normal, but heart auscultation revealed gallops with a loud P2 component of the second heart

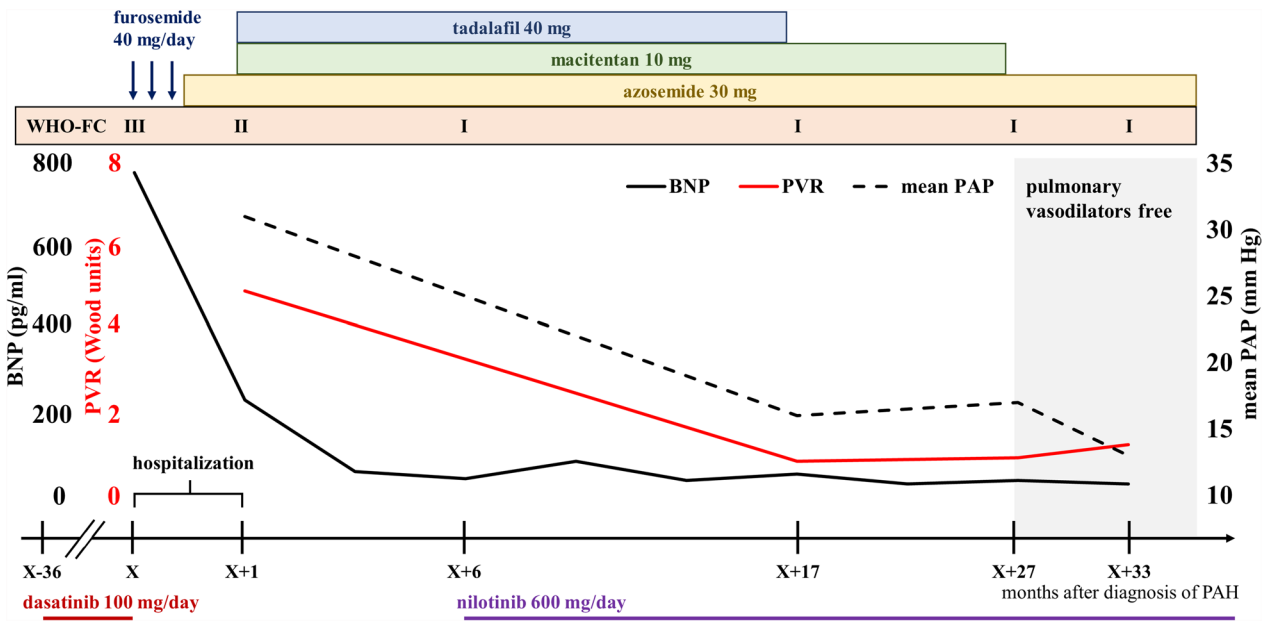

Fig. 1 Changes in the patient's clinical course over time showing the cardiopulmonary parameters and history of PAH-specific therapy. *BNP* brain natriuretic peptide, *PAH* pulmonary arterial hypertension, *PAP* pulmonary arterial pressure, *PVR* pulmonary vascular resistance

sound. The patient's symptoms were classified as with the World Health Organization functional class (WHO-FC) III.

Chest X-ray showed cardiomegaly with bilateral pleural effusion (Fig. 2A). Echocardiography demonstrated pericardial effusion, right atrial area of 23.1 cm^2 (normal reference value, < 18 cm^2), and estimated systolic pulmonary arterial pressure (PAP) of 63 mmHg (normal reference value, ≤ 30 mmHg), and preserved ejection fraction with mild apical hypertrophy, suggesting the presence of underlying heart failure with preserved ejection fraction (HFpEF) (Fig. 2B). Inverted T waves in lead II, III, aVF, and all precordial leads, and deep S wave in lead V5 were noted on the electrocardiogram (Fig. 2C). Inverted T waves in the left chest leads possibly indicated mild apical hypertrophy. Laboratory tests for human immunodeficiency virus antigen and autoantibody screening were negative. The patient's brain natriuretic peptide concentration was increased at 778 pg/mL (normal reference value, < 18.4 pg/mL). His serum hemoglobin concentration was 13.2 g/dL, suggesting the presence of slight anemia. Computed tomography demonstrated no evidence of pulmonary embolism or congenital heart disease. Other potential other causes of pulmonary hypertension were not confirmed on pulmonary angiography and lung ventilation-perfusion scintigraphy. These clinical data suggest the presence of decompensated heart failure due to dasatinib-related PAH, possibly worsened by abdominal cellulitis.

Dasatinib was discontinued, and furosemide (40 mg daily) and an appropriate antibiotic were initiated; 3 weeks later, the patient's fatigue had significantly improved, but there was still mild exertional dyspnea equivalent to WHO-FC II. Right heart catheterization (RHC) demonstrated the high mean PAP of 31 mmHg (normal reference value, < 20 mmHg), high pulmonary vascular resistance (PVR) of 4.92 Wood units, and normal pulmonary arterial wedge pressure (PAWP) of 6 mmHg. The patient was finally diagnosed as having intermediate-risk dasatinib-related PAH according to the current guideline for the diagnosis and treatment of pulmonary hypertension [5]. Since the patient's hemodynamics and symptoms were not completely resolved only by discontinuing dasatinib, the upfront combination therapy with the endothelin receptor antagonist, macitentan, at 10 mg daily, and the phosphodiesterase-5 inhibitor, tadalafil, at 40 mg daily, were started. Subsequently, the patient was followed at the outpatient visit every 2–3 months and his dyspnea had rapidly improved to WHO-FC I; 6 months after discontinuing dasatinib, the proportion of BCR-ABL on international scale was increased over 1%. Through the multidisciplinary discussion, nilotinib 600 mg daily was administered to treat

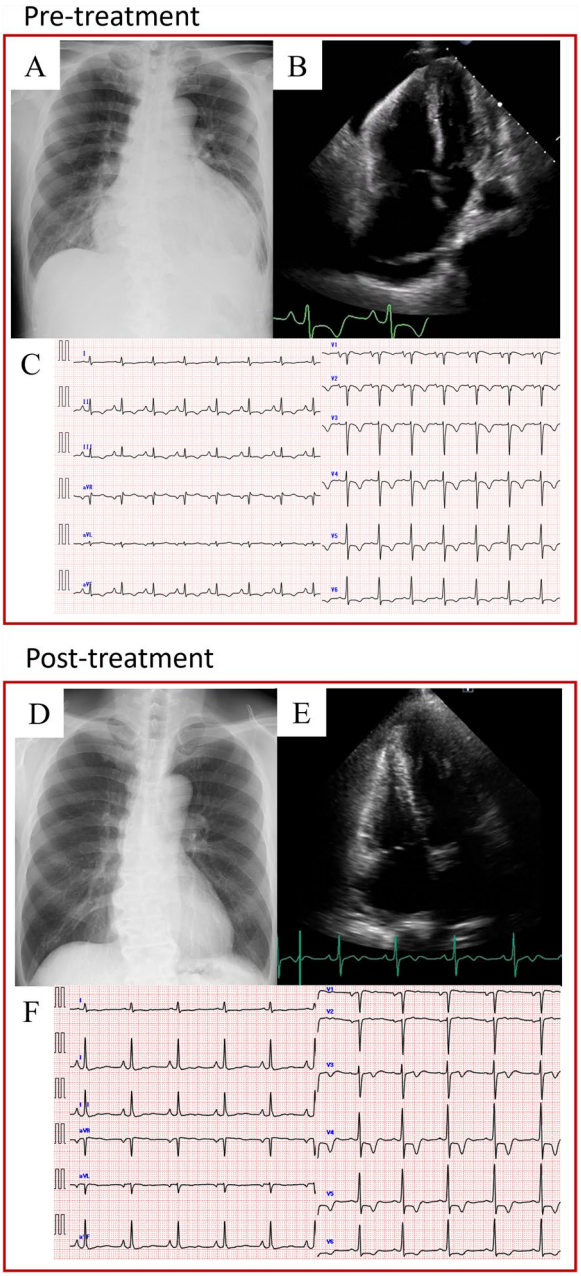

Fig. 2 Chest X-ray, echocardiograph (apical four-chamber view), and electrocardiogram at initial diagnosis (**A**–**C**) and after discontinuation of vasodilators (33 months after the diagnosis) (**D**–**F**)

the recurrent CML. The follow-up RHC after 16 months of upfront combination therapy showed a mean PAP of 15 mmHg, and tadalafil was discontinued. Mean PAP at rest was stable for more than 2 years, and exercise RHC did not demonstrate exercise-induced pulmonary hypertension (EIPH) with mean PAP of 29 mmHg at the peak exercise (normal reference value, < 30 mm Hg),

suggesting preserved pulmonary vascular microcirculation [6]. Given the stability of his pulmonary hemodynamics, macitentan was also discontinued; 6 months after stopping PAH-specific therapy (33 months after diagnosis of PAH), there were no worsening findings of PAH on chest X-ray (Fig. 2D) or echocardiography (Fig. 2E). On the electrocardiogram, signs of the right ventricular hypertrophy, such as inverted T waves in lead II, III, aVF, V1 and V2, and deep S wave in lead V5, were improved. Inverted T waves in V4, V5, and V6 were remained, suggesting the presence of apical hypertrophy of left ventricle (Fig. 2F). Furthermore, follow-up RHC at rest demonstrated the normal PAP of 13 mmHg, PVR of 1.06 Wood units, and PAWP of 4 mmHg. The evaluation during exercise demonstrated that the elevated mean PAP/CO slope of 4.13 mmHg/l/minute (normal reference value, < 3 mmHg/l/minute) without the increase of PVR at peak exercise (1.22 Wood units), suggesting the preserved pulmonary vascular microcirculation (Fig. 3A). Since PAWP/CO slope was elevated to 2.63 mmHg/l/minute, (normal reference value, < 2 mmHg/l/minute) the presence of the early stage of HFpEF was suspected (Fig. 3B). The 6-minute walking distance and pulmonary function tests showed improvement with treatment and remained at normal levels after withdrawing PAH-specific therapy. At 2-year follow-up, the patient has remained stable without any signs of recurrent CML and worsening PAH. Changes of hemodynamics and other parameters were listed in Table 1.

Discussion

We presented the details of a patient with dasatinib-related PAH who was successfully managed with exercise hemodynamic evaluation. The novel learning point of the present case is that preserved pulmonary vascular microcirculation in exercise RHC can serve as a guideline for withdrawing pulmonary vasodilators.

Dasatinib-related PAH is a rare but critical complication, and the cornerstone of the treatment is discontinuing the offending drug and substituting alternative agents [1, 2]. Recent animal studies suggested that dasatinib causes endothelial cell dysfunction by increasing the production of reactive oxidant-independent Src family kinases, which is leading to less hypoxic vasoconstriction and subsequently impaired endoplasmic reticulum function [8]. However, the detailed mechanism underlying dasatinib-related PAH remains unclear. Therefore, which tyrosine kinase inhibitors should be initiated in place of dasatinib is unknown. In the present case, nilotinib was used as a substitute for dasatinib in the treatment of relapsed CML through multidisciplinary discussion.

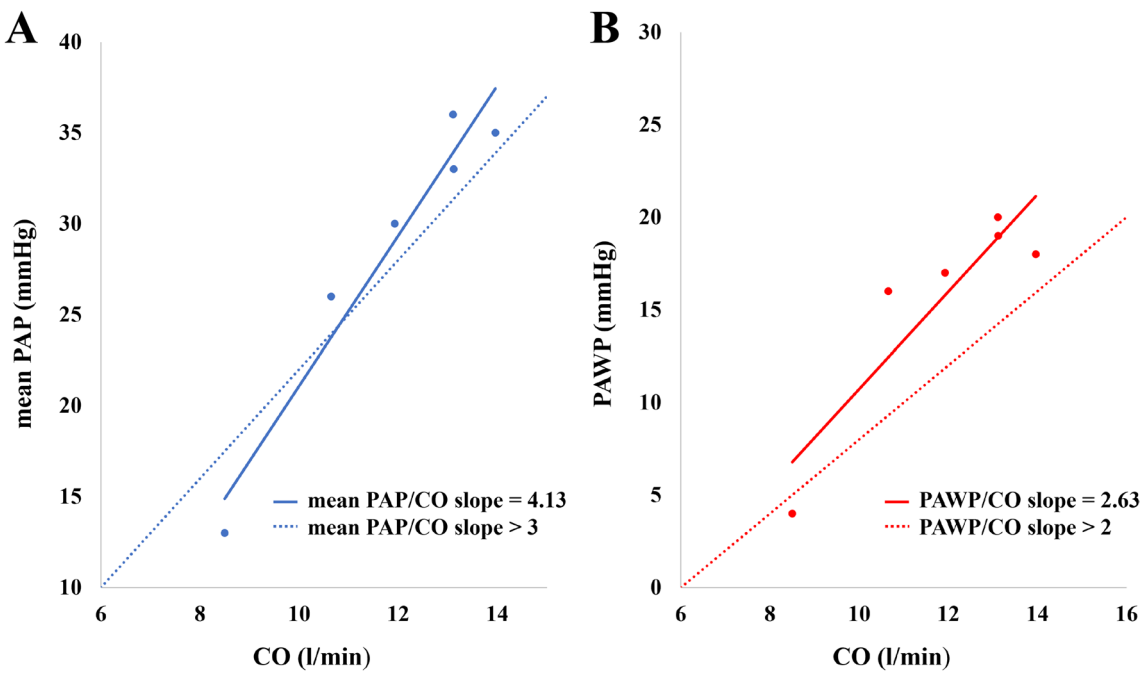

Fig. 3 The mean pulmonary artery pressure (PAP)–cardiac output (CO) relationship (**A**) and the pulmonary artery wedge pressure (PAWP)–CO relationship (**B**) during exercise after discontinuing pulmonary arterial hypertension-specific therapy. The blue dotted line represents a mean PAP/CO slope = 3 mmHg/L/minute. The red dotted line represents a PAWP/CO slope = 2 mm Hg/L/minute

Table 1 Hemodynamics at initial diagnosis and before and after discontinuation of vasodilators

	Initial (X + 1)	Before discontinuation of vasodilators (X + 27)		After discontinuation of vasodilators (X + 33)	
	Rest RHC	Rest RHC	Exercise RHC	Rest RHC	Exercise RHC
RA (mmHg)	4	2		2	
RV (mmHg)	50/1 edp 6	32/0 edp 4		26/0 edp 4	
PAP (mmHg)	49/20 (31)	27/8 (17)	32/26 (29)	26/8 (13)	58/10 (35)
PAWP (mmHg)	6	8		4	18
CO (l/minute)	5.08	9.91		8.5	13.96
CI (l/minute/m^2)	2.71	5.28		4.58	7.52
PVR (Wood units)	4.92	0.91		1.06	1.22
mean PAP/CO slope					4.13
PAWP/CO slope					2.63
6MWT (m)	480	520		548	
FVC % predicted	88.5			93.2	
DLco % predicted	71.9			84.8	

CO cardiac output, *DLco* diffusing capacity of carbon monoxide, *edp* end-diastolic pressure, *FVC* forced vital capacity, *mPAP* mean pulmonary arterial pressure, *RA* right atrial pressure, *RHC* right heart catheterization, *RV* right ventricular pressure, *PAP* pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *6MWT* 6-minute walking test

More than one-third of the patients with dasatinib-related PAH were reported to require pulmonary vasodilators after discontinuing dasatinib in a recent report of 21 patients with dasatinib-related PAH [4]. Current clinical guideline suggests reevaluation 3–4 months after discontinuing the suspected drugs for patients with low risk, and recommends the use of vasodilators immediately for patients with intermediate/high risk, but the indication of deescalation of vasodilators are not mentioned after the normalization of pulmonary hemodynamics [5]. A patient with dasatinib-related PAH was reported to experience hemodynamic worsening after withdrawing pulmonary vasodilators, suggesting the difficulty of safely discontinuing PAH-specific therapy.

Exercise hemodynamic evaluation has been recognized as important clinical information for screening and confirming early pulmonary vascular dysfunction [7, 9]. Thus, we used this novel clinical tool as a guideline for withdrawing pulmonary vasodilators in the present case after achieving normal PAP with combination therapy. EIPH is usually considered as exercise mean PAP > 30 mmHg at the cardiac output (CO) < 10 L/minute, or mean PAP/CO slope between rest and peak exercise > 3 mmHg/l/minute [5]. Additionally, PAWP/CO slope > 2 mmHg/l/minute is a sensitive and useful criterion to diagnose HFpEF and determine the etiology of EIPH [10]. After discontinuation of vasodilators, our patient presented EIPH with a mean PAP/CO slope of 4.13 mmHg/l/minute, but a PAWP/CO slope of 2.63 mmHg/l/minute and normal PVR. These findings suggested that the patient's EIPH was not due to pulmonary vascular dysfunction but HFpEF based on apical hypertrophy.

Of note, pulmonary vascular microcirculation was preserved even 2 years after discontinuing all vasodilators. Generally, patients with PAH must continue pulmonary vasodilators to improve their long-term prognosis. However, these vasodilators are very expensive to both patients and the healthcare system, and they may also impair patients' quality of life owing to the related adverse effects. Therefore, avoiding the long-term use of pulmonary vasodilators is clinically relevant from the perspective of patients' quality of life and healthcare costs. Considering that exercise RHC may have the potential to confirm the feasibility of ceasing vasodilators, exercise hemodynamic evaluation of pulmonary microcirculation can be used as a guideline for withdrawing pulmonary vasodilators safely in the management of patients with dasatinib-related PAH.

This report has limitations. First, we did not perform the exercise stress test at the initial RHC because the patient's mean PAP at rest satisfied the criteria for PAH. Thus, we cannot rule out the possibility of underlying left ventricular diastolic dysfunction at the first assessment of the acute heart failure. Second, a close follow-up RHC could not be performed after initiation of pulmonary vasodilators because of the pandemic of SARS-CoV-2 virus restricting non-urgent hospitalizations. Third, given the limited evidence supporting the discontinuation of pulmonary vasodilators on the basis of normal exercise hemodynamics, performing additional exercise RHC

may increase treatment costs for patients with dasatinib-related PAH, making the discontinuation of vasodilators a significant challenge. Fourth, the treatment response of patients with dasatinib-related PAH may be different individually. There may be potential beneficial effects from our patient discontinuing dasatinib soon after the dyspnea was presented, and vasodilators were administrated before the pulmonary vessels became irreversible, resulting in vasodilator-free remission of PAH. Fifth, we did not perform exercise stress echocardiography because it is challenging to determine whether the cause of PH is related to the left heart or the pulmonary vasculature, as echocardiography provides only an indirect assessment.

Conclusions

Our report suggests that the evaluation of pulmonary microcirculation by exercise RHC might be useful for withdrawing PAH medications and lead to good clinical outcomes in patients with dasatinib-related PAH.

Abbreviations

CML	Chronic myeloid leukemia
CO	Cardiac output
EIPH	Exercise-induced pulmonary hypertension
HFpEF	Heart failure with preserved ejection fraction
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PAWP	Pulmonary arterial wedge pressure
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
WHO-FC	World Health Organization functional class

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Author contributions

SY and TH conceived of the case report and drafted the manuscript; YS, YK, SF, and MK analyzed and interpreted patient's data; MK provided patient's information; and SY, SO, KF, and MI reviewed manuscript. All authors critically reviewed and revised the manuscript draft and approved the final version for submission.

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Availability of data and materials

Nearly all relevant data are presented in the manuscript.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Keio University hospital. We obtained informed consent from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

Authors declare no conflicts of interest.

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